Peer Review File

Responses to the comments of Reviewer A

1. "The topic is interesting and the manuscript is well-written."

Response: Thank you for accepting the academic value conveyed by this paper. We are grateful for your time and patience.

2. "Pylorus-preserving pancreaticoduodenectomy was performed in only 10 patients, while Whipple operation was the procedure of choice in the majority of patients: this is due to Institution's preference?"

Response: This is an excellent question. Obstructive jaundice often appears in the early stage of carcinoma of the papilla of Vater (CPV) [1], which makes it easier to be identified than in pancreatic tumors. Therefore, invasion of the duodenal bulb or pylorus is very rare, Pylorus-preserving pancreaticoduodenectomy (PPPD) is also a surgical option. PPPD has been reported to improve postoperative nutritional status. However, one study of ours showed that PPPD increased the incidence of delayed gastric emptying [2]. Consequently, PPPD was performed in only 10 selected patients.

3. "I think that may be interesting to know which nodal station were involved by the tumor"

Response: We agree with the comment and have added the sentences as follows: "In the posterior or anterior pancreaticoduodenal, hepatoduodenal ligament, right celiac and right side of superior mesenteric artery, rates of nodal involvement were 34% (32/94), 12% (11/94), 7% (7/94) and 22% (21/94), respectively. Para-aortic nodes had no metastases." (**Revised Page 6, Line 16-19).**

4. "The section Discussion is too long and should be shortened (especially the section regarding EUS and IDUS diagnosis)"

Response: We agree that the evaluation of the efficacy of EUS/IDUS is too long and not based on a part of our data. This section has been shortened. We deleted the sentences as follows: "EUS can distinguish the different layers of the gastrointestinal wall so as to accurately determine the depth of tumor invasion, and the accuracy rate for diagnosing the extent of duodenal invasion in CPV has been reported to range from 56% to 83% by EUS" (**Revised Page 9, Line 28); "**therefore, IDUS is considered to be a highly accurate modality to visualize the depth of duodenal invasion in CPV. Itoh

et al. classified duodenal invasion by IDUS as follows: d0, tumors limited to the muscle layer of the sphincter of Oddi; d1, tumors invading the duodenal submucosal layer; d2, tumors invading the duodenal muscularis propria layer; and panc(+), tumors invading the pancreas. The diagnostic accuracy was 100%, 92.3%, 100%, and 75% in d0, d1, d2, and panc(+), respectively.**"(Revised Page 10, Line 8).**

Nevertheless, we don't think this section can be completely deleted for two main reasons. First, the stratification of duodenal invasion proposed in our study is based on the diagnostic ability of EUS/IDUS (mentioned in **Revised Page 10, Line 3-7**), so as to achieve an accurate preoperative diagnosis of the depth of duodenal invasion. Second, our conclusion offers a possible indirect approach to obtain an accurate preoperative diagnosis of lymph node metastasis, and this section is the bridge connecting theory and clinical application. In addition, it is also indispensable to the logical structure of the article.

Responses to the comments of Reviewer B

1. "Why have you not considered the Tis? They are present in the TNM classification and could be part of your stage I (depth of duodenal invasion). This could be at the base of the difference you founded between you proposed classification and the pT"

Response: This is an excellent question. We did not consider the Tis in this study for three reasons. First, there are no Tis cases in our study. Second, obstructive jaundice often appears in the early stage of CPV [1], which makes it easier to be identified than in pancreatic tumors. Therefore, a considerable number of patients including stage Tis may choose local resection at the beginning rather than radical PD. Third, the stratification of duodenal invasion proposed in our study is based on the diagnostic ability of EUS/IDUS (mentioned in **Revised Page 10, Line 3-7**), so as to achieve an accurate preoperative diagnosis of the depth of duodenal invasion. EUS/IDUS cannot distinguish Tis from T1a at present. Our layer I (depth of duodenal invasion) actually contains stage Tis and T1a (AJCC 8th edition).

2. "Actually, excluding pT from your multivariate analysis for collinearity problem (very correct from a statistical point of view) you have no data to sustain the superiority of you proposed classification. You can utilize more specific statistical approach to see if the predictive model created with your classification is better than the one create with the pT, if it works you can stay with your conclusions (even if you still will require a testing external population) otherwise they are not supported by data (Figure 2 for a stratification purpose shows a better curve that figure 3 even without the Tis)."

Response: This is an excellent question. When performing multivariate regression analysis, the collinearity caused by correlated factors is an important problem that needs to be solved. To eliminate the possible collinearity, we chose a stepwise method in multivariate regression, which had been mentioned in Statistical analysis. In order to evaluate prediction accuracy of the model between pT stage and our classification, we have conducted ROC tests on them and have obtained AUC values, which is shown in new added **Figure 4**. The results indicated that the predictive model created with our stratification is better than the one created with the pT. To further clarify this question, we have added the sentences as follows: "ROC tests were used to assess the prediction accuracy of the model." (**Revised Page 5, Line 25-26**); "ROC test showed that the prediction accuracy of model based on duodenal invasion (AUC = 0.72) was better than the one based on pT stage (AUC = 0.69)." (**Revised Page 7, Line 22-24**); "ROC test further verified the conclusion (**Fig. 4**)." (**Revised Page 11, Line 4-5).**

In order to better illustrate censored and endpoint data in the Kaplan-Meier curve, we have added the "number of patients at risk" in newly updated figures and have improved the parameter setting of the censored data with the assistance of a professional statistician Chen Ru (Shanghai Jiaotong University, China) (**Figure 1-3**).

3. "The evaluation of efficacy of IDUS in not part of your data. You wrote an original article and not a literature review or a position paper. In my opinion you shouldn't use so much of your discussion on the topic and couldn't put statement of this technique on the conclusions."

Response: We agree with the comment that the evaluation of the efficacy of IDUS is too long and not based on a part of our data. This section has been shortened. Nevertheless, we don't think this section can be deleted for two main reasons. First, the stratification of duodenal invasion proposed in our study is based on the diagnostic ability of EUS/IDUS (mentioned in **Revised Page 10, Line 3-7**), so as to achieve an accurate preoperative diagnosis of the depth of duodenal invasion. Second, our conclusion offers a possible indirect approach to obtain an accurate preoperative diagnosis of lymph node metastasis, and this section is the bridge connecting theory and clinical application. In addition, it is also indispensable to the logical structure of the article.

4. "I think that the proposal of ampullectomy for pT1 restricted to the mucosa could be a speculation in your discussion, but with the results and data you provide could not be the aim of your work, or better of this work that is not a systematic review on the topic or a comparison of the two technique with long term outcomes."

Response: This is an excellent question. We agree that the comparison of two techniques is not directly based on a part of our data. Nevertheless, we believe that our conclusion offers a possible indirect approach to obtain an accurate preoperative diagnosis of lymph node metastasis so as to offer some surgical guidelines for patients suitable, which is the bridge connecting theory and clinical application. Consequently, focusing on this subject can better arouse readers' interest and better demonstrate clinical value, and it is also more suitable for the translational research theme in the Journal of Translational Cancer Research.

5. "Minor revisions: page 2 and after: in my opinion you should clarify if with local resection you refer to an ampullectomy and also if a transduodenal surgical one or and endoscopic or both."

Response: We agree with the comment and have added the words as follows: "including endoscopic or transduodenal papillectomy" (**Revised Page 2, Line 23).**

6. "Minor revisions: page 4: enlist as surgical data some major pathological characteristic of the tumor could be misleading for the reader. Usually surgical data are time of the operation blood loss approach conversion and so on. I'd suggest you to review you collected data's subgroups."

Response: This is a good question. The subject of the study focused on the relationship between clinicopathological factors and lymph node metastasis, and further analyzed whether these factors have an impact on the prognosis. Factors related to surgery do not conform this subject. In order to make the article more refined, we did not show this part of the data.

Responses to the comments of Reviewer C

1. "Please could Authors better explain preoperative management of patients (radiological management and Endoscopic management)."

Response: Given that the data supporting the role of adjuvant therapies are limited [3], preoperative or postoperative chemo-radiotherapy is not recommended in our center. Consequently, this part of the data is not available. The subject of the study focused on the relationship between clinicopathological factors and lymph node metastasis, and further analyzed whether these factors have an impact on the prognosis. Data related to preoperative endoscopic management do not conform this subject. In order to make the article more refined, we did not show this part of the data.

2. "Please could Authors clarify the Oncological Management, if present, pre and post operation"

Response: Given that the data supporting the role of adjuvant therapies are limited [3],

preoperative or postoperative chemo-radiotherapy is not recommended in our center. Consequently, this part of the data is not available.

References

[1]   Abdullah SA, Gupta T, Jaafar KA, Chung YF, Ooi LL, Mesenas SJ. Ampullary carcinoma: effect of preoperative biliary drainage on surgical outcome. World J Gastroenterol. 2009. 15(23): 2908-12.

[2]   许胜, 俞文隆, 张永杰. 保留幽门的胰十二指肠切除与标准胰十二指肠切除术后胃排空延迟的对比研究. 中华临床医师杂志（电子版）. 2013. (24): 11358-11360.

[3]   Sikora SS, Balachandran P, Dimri K, et al. Adjuvant chemo-radiotherapy in ampullary cancers. Eur J Surg Oncol. 2005. 31(2): 158-63.